P.N. Lee

Environmental Tobacco Smoke and Mortality

A Detailed Review of Epidemiological Evidence Relating Environmental Tobacco Smoke to the Risk of Cancer, Heart Disease and Other Causes of Death in Adults Who Have Never Smoked

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Contents

	Index to Tables	X
	Preface	XV
	Acknowledgements	XX
1	**Introduction**	
1.1	Background and Objectives	1
1.2	Terms of Reference	2
1.3	Structure of This Book	3
1.4	Problems of Inference from Epidemiological Studies	4
1.5	Dosimetric Considerations	4
1.6	Misclassification of Active Smoking Status	7
2	**The 53 Studies**	
2.1	Introduction	9
2.2	Prospective Studies	9
2.2.1	American Cancer Society Million Person Study – Garfinkel I	9
2.2.2	Japanese Study – Hirayama	11
2.2.3	West of Scotland Study – Hole	15
2.2.4	Alameda County Study – Reynolds	18
2.2.5	Rancho Bernardo Study – Garland	19
2.2.6	Multiple Risk Factor Intervention Trial – Svendsen	20
2.2.7	Washington County Study – Sandler II	22
2.2.8	Amsterdam Study – Vandenbroucke	25
2.2.9	Georgia Study – Humble II	25
2.2.10	Californian Seventh-Day Adventists Study – Butler	26
2.3	Case-Control Studies of More than One Disease	27
2.3.1	United Kingdom Study – Lee	27
2.3.2	North Carolina Study – Sandler I	29
2.3.3	Erie County Study of Cancer of All Sites – Miller	32
2.4	Case-Control Studies of Lung Cancer	34
2.4.1	Japanese Atomic Bomb Survivors Study – Akiba	34
2.4.2	Southern Swedish Study – Axelson	35

2.4.3	Colorado Study of Adenocarcinoma – Brownson	36
2.4.4	Texas Study – Buffler	36
2.4.5	First Hong Kong Study – Chan	37
2.4.6	Louisiana Study – Correa	38
2.4.7	Shanghai Study – Gao	39
2.4.8	New Jersey/Ohio Study – Garfinkel II	40
2.4.9	Tianjin Study – Geng	42
2.4.10	New Mexico Study – Humble I	44
2.4.11	Kanagawa Study – Inoue	45
2.4.12	First New York Study – Kabat I	47
2.4.13	Third New York Study – Kabat III	48
2.4.14	Second Athens Study – Kalandidi II	49
2.4.15	Nara Study – Katada	51
2.4.16	German Study – Knoth	52
2.4.17	Second Hong Kong Study – Koo	53
2.4.18	Third Hong Kong Study – Lam I	55
2.4.19	Fourth Hong Kong Study – Lam II	56
2.4.20	Shanghai Study – Li	57
2.4.21	Armadale Study – Lloyd	57
2.4.22	Swedish Study – Pershagen	58
2.4.23	Nagoya Study – Shimizu	59
2.4.24	Osaka Study – Sobue	60
2.4.25	Stockholm Study – Svensson	62
2.4.26	Athens Study – Trichopoulos	63
2.4.27	Second New York Study – Varela	65
2.4.28	Harbin Study of Adenocarcinoma – Wang	68
2.4.29	Los Angeles Study – Wu	68
2.4.30	North-East China Study – Wu-Williams	69
2.4.31	New Jersey Study – Ziegler	72
2.5	Case-Control Studies of Bladder Cancer	73
2.5.1	Canadian Study – Burch	73
2.5.2	US Study – Kabat II	73
2.6	Case-Control Studies of Cervix Cancer	75
2.6.1	Gothenburg Study – Hellberg	75
2.6.2	Utah Study – Slattery	75
2.7	Case-Control Studies of Heart Disease	77
2.7.1	Chinese Study – He	77
2.7.2	Utah Study – Martin	79
2.7.3	US Study – Palmer	79
2.8	Case-Control Study of Chronic Obstructive Pulmonary Disease	80
2.8.1	Greek Study – Kalandidi I	80
2.9	Case-Control Study of Stroke	82
2.9.1	Australian Study – Donnan	82

3 Lung Cancer

3.1	Selection of Studies for Detailed Consideration	83
3.2	Features of the 29 Studies Included	83
3.2.1	Study Design	83
3.2.2	Location	84
3.2.3	Time of Death/Diagnosis	84
3.2.4	The Cases	84
3.2.5	The Controls	88
3.2.6	Sources of Information	93
3.2.7	Non-Response	95
3.2.8	Indices of ETS Exposure	95
3.2.9	Smoking Status of the Subjects	98
3.2.10	Confounding Variables	101
3.3	Summary of Results from the 29 Studies	101
3.3.1	Main Index – Spouse Smoking or Nearest Equivalent	101
3.3.2	Histological Type of Lung Cancer	109
3.3.3	Level of Exposure	111
3.3.4	Variation in Relative Risk According to Other Factors	113
3.3.5	Other Indices of ETS Exposure	115
3.3.6	'Attributable Risk' from ETS Exposure	119
3.3.7	Comparability of Associations with ETS Exposure and Active Smoking	123
3.4	Interpretation of the Findings	124
3.4.1	The Main Findings	124
3.4.2	Plausibility	125
3.4.3	Explanations to Be Considered	127
3.4.4	Misclassification of Diagnosis	128
3.4.5	Misclassification of ETS Exposure	129
3.4.6	Lack of Comparability of Cases and Controls	130
3.4.7	Other Study Weaknesses	132
3.4.8	Confounding	133
3.4.8.1	Age	133
3.4.8.2	Marital Status	134
3.4.8.3	Other Confounding Factors	135
3.4.8.4	Conclusions Regarding Confounding	142
3.4.9	Misclassification of Active Smoking Status	142
3.4.9.1	The Problem	142
3.4.9.2	Major and Minor Sources of Bias	143
3.4.9.3	What Level of Misclassification Would Be Needed to Explain the Observed Associations of Spouse Smoking with Lung Cancer?	146
3.4.9.4	Evidence on Extent of Misclassification	150
3.4.9.5	Evidence on Extent of Smoking Habit Concordance	158
3.4.9.6	Conclusions Regarding Misclassification	162
3.4.10	Publication Bias and Other Issues in Meta-Analysis	164
3.5	Overall Assessment of the Evidence on ETS and Lung Cancer	166

4 **Other Cancers**

4.1 Studies Providing Data 168

4.2 Results 168
4.2.1 Weaknesses of Some Studies 168
4.2.2 Overall Risk 169
4.2.3 Lip, Oral Cavity and Pharynx 172
4.2.4 Digestive System 173
4.2.5 Respiratory Sites Other Than the Lung 174
4.2.6 Bone, Connective Tissue and Skin 174
4.2.7 Breast 175
4.2.8 Female Genital System 176
4.2.9 Male Genital System 178
4.2.10 Urinary Tract 179
4.2.11 Eye, Brain and Nervous System 179
4.2.12 Endocrine Glands 180
4.2.13 Lymphatic and Haematopoietic Tissue 180
4.2.14 Other Cancer 181

4.3 Discussion and Conclusions 181

5 **Heart Disease**

5.1 Studies Providing Data 184
5.2 Features of the Studies Included 184
5.3 Results 186
5.4 Discussion and Conclusions 193

6 **Other Diseases**

6.1 Studies Providing Data 197

6.2 Results 197
6.2.1 Tuberculosis 197
6.2.2 Diabetes 197
6.2.3 Cerebrovascular Disease 198
6.2.4 Respiratory Diseases 199
6.2.5 Diseases of the Digestive System 200
6.2.6 Gastro-Intestinal Ulcer 200
6.2.7 Cirrhosis of the Liver 201
6.2.8 Diseases of the Genito-Urinary System 201
6.2.9 Accidental Causes of Death 201
6.2.10 Suicide 201
6.2.11 Other Diseases 201

6.3 Discussion and Conclusions 202

7 **Overall Risk of Mortality**

7.1 Studies Providing Data 203
7.2 Results 203
7.3 Discussion and Conclusions 207

8 **Conclusions** 208

References 210
Subject Index 219

5 Heart Disease

5.1 Studies Providing Data

Eleven studies have provided information on the relationship of ETS to risk of cardiovascular disease. Seven of these are prospective studies, 5 conducted in the USA (Butler, Garland, Humble II, Sandler II, Svendsen), 1 in Japan (Hirayama) and 1 in Scotland (Hole). Four are case-control studies, 2 in the USA (Martin, Palmer), 1 in China (He) and 1 in England (Lee).

Three prospective studies which have reported results for lung cancer (Garfinkel 1), total cancer (Reynolds) or all-cause mortality (Vandenbroucke) have not reported results for heart disease. While the numbers of deaths would not be substantial for the last 2 studies, the fact that the first, the American Cancer Society million person study, has not provided information is a wastage of resource. This study alone would certainly have had data on more deaths/cases than all the 11 published studies combined.

5.2 Features of the Studies Included

It should be noted that very little information is available for 3 of the 11 studies considered: the prospective study of Butler, and the case-control studies of Martin and Palmer for which the only published data consist of abstracts.

The number of deaths/cases in some studies is very small. There are 4 studies with extremely small numbers (Svendsen, 13; Garland, 19; Martin, 23; He, 34), 4 with quite small numbers (Humble II, 76; Butler, 80; Hole, 84; Lee, 118), and 1 (Palmer, 336 in ever smokers and never smokers combined) which, though of moderate size, has not presented findings in a form to allow proper evaluation. Considering the prevalence of heart dis-

ease among never smokers – very much higher than from lung cancer – it is surprising that by now there are only 2 published studies for reporting results based on reasonably substantial numbers of deaths/cases (Hirayama, 494; Sandler II, 1,358).

Of the 7 prospective studies, 4 involved study subjects attending for an examination during which blood pressure, cholesterol and body mass index were measured. It is unfortunate that neither of the 2 substantial studies collected information on these classical risk factors for heart disease. The factors used by the authors for adjustment – occupation by Hirayama, and schooling, housing quality and marital status by Sandler II – are not those which first occur as being most relevant in a study of heart disease.

Some of the studies have problems regarding representativeness of the subjects. Thus, in both the Garland and Hole studies, about 20% of the population did not attend for examination, with a possibility of bias if failure to attend was associated both with ETS exposure and risk of death from heart disease. In the large Sandler II study, only deaths in Washington County were recorded, again imparting a danger of bias if ETS is associated with the chance of migration out of the county. The Svendsen study was based on the well-known Multiple Risk Factor Intervention Trial, which involved people at very high risk of heart disease based on their smoking, blood pressure and cholesterol levels. Since the paper concerned never smokers, all the subjects involved most probably exhibited abnormally high blood pressure and/or cholesterol levels. The Butler study involved Seventh-Day Adventists, an atypical population with regard to many variables.

The 2 studies which provided data on by far the largest number of deaths are both open to criticism, as detailed in sections 2.2.2 (Hirayama) and 2.2.7 (Sandler II), and also in section 4.2.1. It is interesting to note that both studies have published inconsistent results for women. In 1981, Hirayama presented results showing no association of heart disease with husband smoking, based on follow-up of his population to 1979. In 1984, he reported results which showed a significant association, based on follow-up of his population to 1981. These results implied an implausibly strong relationship of heart disease to smoking by the husband when deaths occurring in 1979–81 were considered (a fact pointed out by Lee in correspondence in the *New Zealand Medical Journal* [26, 27]). As a result, Hirayama published revised figures for follow-up to 1979, indicating that the data published in 1981 were incorrect.

Helsing et al. [40] and Sandler et al. [43] have both presented (in Table 4 of each paper) results for risk of arteriosclerotic heart disease in relation to ETS exposure. Based on identical numbers of deaths and stated adjustment factors, the reported relative risks and confidence limits for men were identical. Inexplicably, however, this was not the case for women, where relative risks and confidence limits both varied. Given the relatively larger contribution of the Hirayama and Sandler II results to the overall number of heart disease cases studied, such differences in reported findings are rather disconcerting.

5.3 Results

Table 5.1 summarizes results for exposure to ETS from the spouse or in the household. Before considering the findings, some points are worth noting:

(i) As far as can be ascertained, all the relative risks are for never smokers.

(ii) The index was based on smoking by the spouse in 7 studies (Butler, Garland, He, Hirayama, Humble II, Lee, Svendsen), only married women being considered, except perhaps in the Chinese study where single women were included with the wives of non-smoking husbands. In 2 studies (Martin, Palmer) the index used is not known. The Hole study compared people living at the same address as a study participant who had ever smoked with people who lived at the same address as a study participant who had never smoked, with no other study participant at that address ever having smoked. The Sandler II study used a complex index of exposure, but for the results in Table 5.1 it amounted to a comparison of people living in the household where some adult had ever smoked with people in a household where no adult had ever smoked.

(iii) When a study has presented different findings at different time points for apparently the same comparison, the later publication has been used, namely, Hirayama [23] and not his 1981 paper [2], and Sandler et al. [43] and not Helsing et al. [40].

(iv) If the authors have presented adjusted relative risks these have normally been given in Table 5.1. There are some exceptions. First, the relative risk of 14.9 by Garland et al. [38], adjusted for age, systolic blood pressure, total cholesterol, obesity index and years of marriage,

Table 5.1 Heart disease risk in never smokers in relation to spouse/household smoking

Study	Sex	Cases		Relative risk (95% limits)	Factors[1] adjusted for
		U	E		
Butler	F	20	60	1.05 (0.65–1.70)	Age
Garland	F	2	17	3.51 (0.80–15.3)	None[2]
He	F	9	25	1.50	See text
Hirayama	F	118	376	1.15 (0.94–1.42)	Age of wife
Hole					
Gillis et al.	F	2	19	3.56 (0.83–15.4)	None[3]
	M	18	14	1.30 (0.64–2.64)	None[3]
Hole et al.	M+F	30	54	2.01 (1.21–3.35)	Age, sex, class, BP, chol, BMI
Humble II	F	27[4]	49	1.59 (0.99–2.57)	Age, sex, BP, chol, BMI
Lee	F	22	55	0.97 (0.56–1.69)	None[3]
	M	26	15	1.34 (0.64–2.80)	None[3]
Martin	F	— 23 —		2.6 (1.2–5.7)	None[2]
Palmer	F	— ? —		1.2 (significance unknown)	Not known
Sandler II	F	437	551	1.19 (1.04–1.36)	Age, schooling, housing, marital status
	M	248	122	1.31 (1.05–1.64)	
Svendsen	M	8	5	2.23 (0.72–6.92)	Age, BP, chol, wt, drinks, education

U = Unexposed; E = exposed.
[1] BP = blood pressure; chol = cholesterol; BMI = body mass index; wt = weight.
[2] See text.
[3] Adjustment for age had little effect, and adjusted 95% limits could not be calculated.
[4] Numbers of cases are approximate, based on age-adjusted rates.

has not been used. It would be incredibly unstable (estimated 95% limits, about 0.2–500), since it is probably impossible to adjust properly for multiple factors with so few deaths. Mantel [pers. commun.] has also said that 14.9 was an error, the appropriate value being $\log_e(14.9)$ or 2.71!

Secondly, unadjusted relative risks have been used for the individual sex results from the Hole study (published in Gillis et al [29]), since age standardization had very little effect and relative risks could only be properly calculated for the unadjusted data.

(v) The relative risk given in the He study [102], a case-control study in which there was matching on age, race, place of residence and occupation, is adjusted for previous and family history of hypertension, family history of coronary heart disease, amount of exercise, history of drinking, and hypercholesterolaemia. Confidence limits could not be calculated, but the relative risk was stated to be significant ($p < 0.01$), but this seems not to be true (see section 2.7.1).

(vi) The results presented in Table 5.1 for the Hirayama study are for ischaemic heart disease. Hirayama [20] notes that no significant relationship was seen between spouse smoking and risk of 'other heart disease' (undefined), based on 680 deaths, or risk of hypertensive heart disease, based on 226 deaths. Relative risk estimates were not provided for these two disease categories.

Table 5.1 provides 4 independent relative risk estimates for men and 10 for women, 13 of which are greater than 1, with 4 of them significant: both the male and female estimates for the Sandler II study, and the female estimates for the He and Martin studies. Hole also showed a significantly increased relative risk when results for the sexes were combined. Although an overall estimate of relative risk (as for example calculated by Wells [7]) is probably of little meaning given the extreme variability in study designs and populations involved, the data in this table – considered without regard to study design and a variety of other methodological problems – indicate a weak association between exposure to ETS from the spouse or in the household and risk of heart disease.

Five of the 11 studies provided some information on risk of coronary heart disease and extent of exposure to ETS from the spouse or in the household (Table 5.2). The Hirayama and He studies both showed evidence of a dose-response relationship, with a significant ($p < 0.05$) trend and elevation in risk for women whose husbands smoked 20 or more cigarettes a day. The Hole and Svendsen studies also showed the highest risk in the highest exposure group, though here numbers of deaths were small and the trend statistic was not significant. In the large Sandler II study there was no evidence of a relationship of risk to ETS exposure in either sex, risk of heart disease being similar in those classified as exposed to light or heavy ETS exposure.

Table 5.2 Heart disease risk in never smokers in relation to extent of spouse/household smoking

Study	Sex	Exposure	Cases	Relative risk	Factors adjusted for
Hirayama	F	Husband:			
		never smoker	118	1.00	Age of wife
		ex-smoker or current			
		1–19 cigs/day	240	1.08	
		current 20+ cigs/day	136	1.30	
He	F	Husband:			Cases and
		never smoked during marriage	9	1.00	controls
		smoked 1–20 cigs/day	12	2.30	matched for
		smoked 21+ cigs/day	13	6.86	age, race, occupation, residence
Hole	F	Household smoking:			
		none	3	1.00	Age
		low	14	2.09	
		high (cohabitant 15+ cigs/day)	16	4.12	
Sandler II		Household exposure (score):			
	F	0 (none)	437	1.00	Age
		1–5 (light)	252	1.20	schooling,
		6+ (heavy)	299	1.27	housing
	M	0 (none)	248	1.00	quality,
		1–5 (light)	56	1.39	marital status
		6+ (heavy)	66	1.24	
Svendsen	M	Wife:			
		did not smoke	8	1.00	None
		smoked 1–19 cigs/day	1	0.90	
		smoked 20+ cigs/day	4	3.21	

Information on heart disease in relation to other indices of ETS exposure is fairly sparse. In the Lee study, subjects were classified on a score ranging from 0 to 12 according to whether they considered they were exposed not at all (0), a little (1), average (2), or a lot (3–12), separately for at home, at work, during travel, and during leisure. No significant relationships were seen, relative risk estimates for scores 0–1, 2–4 and 5–12 being 1, 0.43 and 0.43 in males (based on 30 deaths), and 1, 0.59 and 0.81 in females (based on 36 deaths).

Table 5.3 Effect of adjustment for various factors on estimated relative risk of heart disease in never smokers according to spouse/household smoking

Study	Sex	Adjustment factors	Relative risk (95% limits)
Butler	F	None	1.36 (0.82–2.25)
		Age	1.05 (0.65–1.70)
He	F	Matching factors (age, race, residence, occupation) only	3.52 (1.43–8.65)
		Matching factors, also previous and family history of hypertension, family history of CHD, exercise, drinking, hypercholesterolaemia	1.50
Hirayama	F	None	1.00 (0.81–1.23)
		Age of wife	1.15 (0.94–1.42)
		Age of husband	1.15 (0.93–1.41)
		Age and occupation of husband	1.16 (0.94–1.43)
Hole	F	None	3.56 (0.83–15.4)
Gillis et al.		Age	3.25
	M	None	1.30 (0.64–2.64)
		Age	1.29
Hole et al.	M+F	Age	1.75 (1.10–2.83)
		Age, sex, social class, BP, chol, BMI	2.01 (1.21–3.35)
Humble II	F	Age	1.34 (0.84–2.21)
		Age, BP, chol, BMI	1.59 (0.99–2.57)
Lee	F	None	0.97 (0.56–1.69)
		Age, marital status	0.93
	M	None	1.34 (0.64–2.80)
		Age, marital status	1.24
Sandler II	F	None	0.66 (0.59–0.75)
		Age, housing quality, schooling, marital status	1.19 (1.04–1.36)
	M	None	1.17 (0.95–1.46)
		Age, housing quality, schooling, marital status	1.31 (1.05–1.64)
Svendsen	M	None	2.12 (0.69–6.46)
		Age, BP, chol, wt, drinks/week, education	2.23 (0.72–6.92)

BMI = Body mass index; BP = blood pressure; chol = cholesterol; CHD = coronary heart disese; wt = weight.

In the Svendsen study, a relative risk estimate, adjusted for age and wife's smoking status, of 2.6 ($p = 0.23$; 95% limits, 0.5–12.7) was derived when men whose co-workers smoked were compared with men whose co-workers did not. This result, and that in Table 5.1, was for coronary death. Svendsen also provided results for the end-point fatal or non-fatal coronary event. Here, relative risk estimates were derived for four categories: (a) neither wife nor co-worker smoked, 1.0 (base); (b) co-worker smoked but not wife, 1.0; (c) wife smoked but not co-worker, 1.2; (d) both wife and co-worker smoked, 1.7.

No result was significant. In the study by Butler which, in the AHSMOG cohort, related heart disease risk to the number of years lived and the number of years worked with a smoker, some 'suggestion' or 'indication' of an effect was reported in both sexes, but no detailed results were reported.

No other study provided information on other indices of exposure. In the study by He, relative risks of 1, 1.88, 3.07 and 5.49 were reported in relation to 0, 1–10, 11–20 and 21+ years of ETS exposure, and relative risks, of 1, 1.54, 2.30, 5.07 and 12.67 were reported in relation to 0, 1–199, 200–399, 400–599 and 600+ cigarette-years of smoking by the husband. Both trends were statistically significant ($p < 0.01$).

Leaving aside the Garland study for reasons noted in subsection (iv) above, 7 studies provided some information on the extent to which adjustment for various risk factors affected the estimates of heart disease risk in relation to spouse/household smoking. The results are summarized in Table 5.3.

Two main conclusions can be drawn from this table. First, that in some studies age adjustment made a substantial difference to the relative risk. This effect, which would depend on the design of the study and on the frequency of smoking by age and sex in the country concerned, is evident in the Hirayama study and is also probably a contributor to the large association reported in the Sandler II study.

The second main conclusion is that there is no clear effect from additional adjustment for the classical coronary risk factors. Thus, while the Hole, Humble II – and perhaps the Svendsen – studies showed some increase in relative risk after adjustment, the He study showed a substantial decrease.

Some of the prospective studies cast more light on the possibility of confounding by various risk factors, since they present data comparing exposed and non-exposed women at the start of the study. The results are

Table 5.4 Comparison of heart disease risk factors in ETS-exposed and non-ETS-exposed subjects

Study	Sex	Risk factor		Spouse/household exposure		Significance
				no	yes	
Sandler II	F	School grade (12+)	(%)	33.8	35.4	$p < 0.1$
		Housing index (8–10)	(%)	83.3	81.1	$p < 0.01$
	M	School grade (12+)	(%)	38.0	43.8	$p < 0.01$
		Housing index (8–10)	(%)	83.8	80.4	$p < 0.05$
Garland	F	Years of marriage	Mean	36.0	34.2	$p < 0.1$
		Systolic blood pressure	Mean	140.1	138.2	NS
		Obesity index	Mean	3.50	3.43	NS
		Plasma cholesterol	Mean	225.7	226.7	NS
Svendsen	M	Diastolic blood pressure	Mean	103.1	103.3	NS
		Systolic blood pressure	Mean	150.8	152.3	NS
		Serum cholesterol	Mean	264.4	266.0	NS
		HDL cholesterol	Mean	42.7	43.4	NS
		LDL cholesterol	Mean	167.1	166.5	NS
		Weight (lbs)	Mean	190.4	194.6	$p < 0.05$
		Drinks/week	Mean	7.6	9.7	$p < 0.01$
		Education (years)	Mean	14.2	13.8	$p = 0.05$
		Income ($ 000)	Mean	22.3	22.1	NS

HDL = High density lipoprotein; LDL = low density lipoprotein.

summarized in Table 5.4. Significant differences were seen in respect of weight (ETS-exposed heavier), drinks per week (ETS-exposed drink more), housing index (ETS-exposed worse), and years of education (ETS-exposed more in Sandler II, less in Svendsen), but is not clear that these differences were large enough to cause substantial bias. The Chinese case-control study of He also reported differences in blood fat and apolipoprotein levels according to ETS exposure, but did not attempt to adjust for these in the analysis.

One risk factor which might be relevant, but which was not investigated, was the number of cohabitants. In the Sandler II and Hole studies the index of ETS exposure seemed by its very construction to be correlated with the number of cohabitants. In particular, the Sandler II study would

Table 5.5 Effect of other variables on estimated relative risk of heart disease in never smokers according to spouse smoking

Study	Sex	Variable/level	Relative risk[1] (95% limits)	Factors adjusted for
Hirayama	F	Age of wife:		None
		40–49	0.87 (0.47–1.62)	
		50–59	1.03 (0.72–1.46)	
		60+	1.30 (0.98–1.73)	
		Age of husband:		None
		40–49	1.34 (0.74–2.42)	
		50–59	1.25 (0.81–1.92)	
		60+	1.07 (0.83–1.40)	
		Occupation:		Age of husband
		agricultural worker	1.32 (0.99–1.74)	
		other	0.99 (0.72–1.35)	
Humble II	F	Blacks	1.78 (0.86–3.71)	Age, BP, chol.,
		High social status Whites	1.97 (0.72–5.34)	BMI
		Low social status Whites	0.79 (0.32–1.96)	

BMI = Body mass index; BP = blood pressure; chol = cholesterol.
[1] For wives whose husband smoked compared to those whose husband did not smoke.

have included all people living on their own in the non-exposed group, and both studies were very likely to include people living in homes with many occupants in the exposed group. Since household size may correlate with many facets of disease, it seems to be a statistical error not to adjust for it in analysis.

Two studies provided some information on variation in relative risk according to the level of some risk factors. Results are summarized in Table 5.5, and show how the association with ETS exposure varies by age and occupation in the Hirayama study and by race and social status in the Humble II study. Although the association with spouse smoking is evident only in agricultural workers in the Hirayama study and only in Blacks and high social status Whites in the Humble II study, there is in fact no significant heterogeneity between the relative risk estimates in either study.

5.4 Discussion and Conclusions

Although lung cancer is a rare cause of death in those who have never smoked, heart disease is not, and it is much easier to conduct an adequately large study for heart disease than for lung cancer. Yet there are far more studies of ETS and lung cancer than of ETS and heart disease. It is striking that so many of the latter studies are based on very small numbers of deaths or cases and/or have not been properly reported in the literature.

Only 2 studies are sufficiently large to pick up a moderate increase in risk as statistically significant, and neither is satisfactory. Both lack data on classical heart disease risk factors, such as blood pressure, cholesterol and body mass index, and both have a number of problems that have been referred to in detail earlier. Certainly, neither is a straightforward prospective study conducted according to acceptable methodology, with collection of risk factor data at intervals and essentially complete follow-up of deaths.

Apart from the generally unimpressive nature of the studies that have been conducted, the other circumstance that stands out is that 13 of the 14 sex-specific estimates of relative risk of heart disease for spouse or household exposure in Table 5.1 show a positive (though for the most part not statistically significant) association. In considering this fact, a number of points have to be taken into account:

(i) Active smokers have an increased risk of heart disease, as is clear from numerous epidemiological studies. However, the relative risk is much lower than it is for lung cancer. For example, the 1989 US Surgeon General's report [71] cites results from the latest American Cancer Society prospective study showing that, compared with never smokers, current smokers have relative risks of heart disease of 1.94 in males and 1.78 in females, as compared to relative risks of lung cancer of 22.36 in males and 11.94 in females.

Vapour phase components of cigarette smoke have been implicated in the aetiology of heart disease (rather than particulate phase components for lung cancer [1]), and the relative exposure of ETS-exposed non-smokers as compared with active smokers is substantially higher for vapour phase than for particulate phase components, but the low relative risks for heart disease for active smoking strongly suggest that if ETS does increase risk of heart disease this increase would be quite modest. The six estimates of over 1.5 in Table 5.1 seem difficult to

reconcile with the dosimetry, especially bearing in mind that active smokers have very substantial ETS exposure.

(ii) Heart disease is certainly multifactorial, and many of the risk factors have not been taken into account in many of the studies. Confounding is therefore a possibility, particularly in the 2 studies (Hole, Sandler II), where the index of ETS exposure used was likely to be extremely strongly correlated with household size. While the evidence discussed in Tables 5.3 and 5.4 does not clearly demonstrate important confounding by blood pressure, cholesterol or body mass index it is rather limited and somewhat inconsistent. More evidence is clearly needed on this important potential source of bias.

(iii) Bias due to misclassification of active smoking status is likely to occur, but since the increase in risk in relation to active smoking is relatively so much less for heart disease than for lung cancer, the extent of the bias will be that much smaller. Since the bias is proportional to the excess risk (see section 3.4.9), its magnitude will be only 5–10% of that illustrated in typical situations for lung cancer.

(iv) Publication bias is one major source of bias that can certainly not be excluded as relevant. There are two major reasons for believing this may be an important issue. First, there is a strong tendency in Table 5.1 for the large relative risk estimates to be based on very small studies. From the 13 sex-specific estimates, the rank correlation is highly significantly ($p < 0.05$) negative. Who would bother to try to publish a paper showing no association based on very few deaths?

Secondly, certain studies that could publish findings have not done so. Of particular importance is the fact that the first American Cancer Society study of over a million men and women, which published results for ETS and lung cancer in 1981, has never published results for ETS and heart disease. It is very likely that no association was found. If this were so, it would have a very large effect on the results of any meta-analysis (or consequent estimate of heart disease deaths 'due to ETS').

Mainly because of the problems caused by the strong likelihood of severe publication bias, it cannot be concluded from the existing evidence that ETS is associated with heart disease. The present author understands that the American Cancer Society intends to publish within the next year or so findings related to ETS based on its second large prospective study. It is hoped that results from its first prospective study will also be released. Until there is such evidence, and hopefully also evidence from other studies involving substantial numbers of deaths from heart disease with good

control of confounding and with evidence on ETS exposure from sources other than the spouse or in the home, it is certainly premature to come to any conclusions.

Note Added in Proof

Since this section was completed, Dobson et al. [166] reported results from an Australian case-control study of myocardial infarction and sudden death. Among non-smokers there was no positive relationship of risk to ETS exposure at work in either sex. Nor was there a positive relationship of ETS exposure at home in males. In contrast, in females a significant positive relationship of risk was reported to ETS exposure at home. In this study, data on smoking habits were collected by completely different methods for cases and controls, the potential of bias being underlined by the wide variation in smoking frequency reported in controls according to how and where the data were collected. In addition, virtually no relevant confounding variables were taken into account.